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10/526,073	02/28/2005	Shigekazu Hokazono	HOKAZONO1	8315
1444 7590 06/02/2008 BROWDY AND NEIMARK, P.L.L.C. 624 NINTH STREET, NW SUITE 300 WASHINGTON, DC 20001-5303				
EXAMINER				
RAMIREZ, DELIA M				
ART UNIT		PAPER NUMBER		
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

***ADVISORY ACTION***

1. Claims 1 and 6 are pending.
2. The request for entering amendments to claim 1, submission of a copy of a section of the Molecular Cloning Manual by Sambrook et al., submission of a new sequence listing, and arguments filed on 5/12/2008 under 37 CFR 1.116 in reply to the Final Action mailed on 2/12/2008 are acknowledged. The proposed amendments to the claims will not be entered. While the amendment to the sequence listing would overcome some of the grounds of rejections under 35 USC 112, second paragraph, because SEQ ID NO: 2 in the new sequence listing is a nucleic acid, the proposed amendments to claim 1 do not resolve all the issues regarding the indefiniteness rejection previously applied, do not overcome the previous enablement rejection, and raise new issues which would require further consideration and/or search as discussed below.
3. Amended claim 1 as proposed would remain rejected under 35 USC 112, second paragraph due to the recitation of “nucleic acid hybridizing to the nucleotide sequence of SEQ ID NO: 2”. As indicated in the Final action of 2/12/2008, hybridization occurs between nucleic acid molecules and not between a nucleic acid and a sequence, which is a graphical representation of the order in which nucleotides are arranged in a nucleic acid molecule.
4. Amended claim 1 as proposed would be rejected under 35 USC 112, first paragraph, new matter, since there is absolutely no support for changing the hybridization conditions in the claim from 50 °C to 68 °C or the washing conditions as now recited. The Examiner acknowledges that the specification refers to stringent conditions as “those described in Maniatis et al. (Molecular Cloning: A Laboratory Manual 2<sup>nd</sup> edition, Cold Spring Laboratories, 1989) or the like” (page 21, lines 21-25 of the specification). However there is no statement of incorporation by reference to the teachings of Maniatis et al. There is no indication in the specification that there was a clear intent to incorporate by reference the conditions disclosed in Maniatis et al. Furthermore, there is no disclosure in the specification that explicitly

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indicates 68 °C or the washing conditions as now recited as preferred embodiments of the genus of hybridization conditions. Therefore, Applicant's amendment is deemed an improper incorporation by reference. See 37 CFR 1.57.

5. Amended claim 1 as proposed would be rejected under 35 USC 112, first paragraph, written description and scope of enablement, because the genus of polypeptide encoded by the amended genus of polynucleotides is not adequately described and it would require undue experimentation to enable the entire genus of polypeptides encoded the genus of nucleotides now recited in the claim. While it is agreed that the hybridization conditions now recited would allow for 5.6% mismatching according to the Mcintosh and Wahl equation previously cited ( $5.6\% = 73.6\text{ }^{\circ}\text{C} - 68\text{ }^{\circ}\text{C}$ ), there is no disclosure of a structure/function correlation which would allow one of skill in the art to recognize which of the many polynucleotides encompassed by the genus recited would encode a protein having thermostable ribonuclease H. There is no disclosure as to which 5.6% of the structure of the nucleic acid of SEQ ID NO: 2 can vary and still be able to encode a protein having thermostable ribonuclease H activity. Thus, one cannot reasonably conclude that the teachings of the specification adequately describe the entire genus of polypeptides now recited. See the revised Written Description Training Materials recently published for guidance. With regard to the scope of enablement rejection, the level of mismatching associated with the conditions recited allows for proteins having 36 amino acid changes in the polypeptide of SEQ ID NO: 1 ( $36 = 0.056 \times 636$ ; SEQ ID NO: = 636 nucleotides) as each nucleotide mismatch can potentially affect a codon. Using the previously presented formula to calculate all the possible variants having a specific number of substitutions, the total number of variants of the polypeptide of SEQ ID NO: 1 having 36 substitutions amounts to  $5.8 \times 10^{87}$  variants. Thus, the number of variants to be tested without any guidance as to which variants are more likely to have the recited activity is essentially infinite. This amount of experimentation is undue as the specification has not provided any teaching or suggestion as to the structural features more likely to be associated with the recited function.

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Therefore, one cannot reasonably conclude that the claimed genus of polypeptides is fully enabled by the teachings of the specification and/or the prior art.

6. The rejections previously applied are, therefore, maintained for the reasons of record in view of the non-entry of the proposed amendments.

7. For purposes of Appeal, the status of the claims is as follows:

Claim(s) allowed: 6

Claim(s) rejected: 1

8. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashaat Nashed can be reached on (571) 272-0934. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/Delia M. Ramirez/

Delia M. Ramirez, Ph.D.  
Primary Patent Examiner  
Art Unit 1652

DR  
June 3, 2008